SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Device, Fecal Incontinence, Implanted
Device Trade Name:	Acticon™ Neosphincter
Applicant's Name and Address:	American Medical Systems 10700 Bren Road West Minnetonka, MN 55343
PMA Number:	P010020
Date of Panel Recommendation:	August 17, 2001
Date of Notice of Approval to Applicant:	December 18, 2001

II. INDICATIONS FOR USE

The Acticon™ Neosphincter is an implantable device used to treat severe fecal incontinence in males and females eighteen years and older who have failed, or are not candidates for, less invasive forms of restorative therapy.

III. CONTRAINDICATIONS

This device is contraindicated in patients whom the physician determines to be poor candidates for surgical procedures and/or anesthesia due to physical or mental conditions.

This device is contraindicated in patients with fecal incontinence complicated by an irreversibly obstructed proximal segment of bowel.

This device is contraindicated in patients with an active infection.

IV. WARNINGS AND PRECAUTIONS

Warnings

1. Patients with diabetes, spinal cord injuries, musculoskeletal abnormalities, pre-existing stomas, or open sores in the region of the surgery have an increased risk of infection associated with a prosthesis. Patients who are immunocompromised or immunosuppressed may also be at a higher risk for infection associated with a prosthesis. Appropriate measures should be taken to reduce the likelihood of infection.

   Infection that fails to respond to antibiotic therapy may result in removal of the prosthesis. Infection followed by explantation of the device may result in scarring which may make subsequent reimplantation more difficult.

2. Erosion may be caused by infection, pressure on the tissue, improper cuff sizing, improper balloon selection, tissue damage, and component misplacement. The cuff may erode around the anal canal or through the perianal skin. The control pump may erode through the scrotal or labial skin. The pressure-regulating balloon can erode into the bladder. Failure to evaluate and promptly treat the erosion may result in a substantial worsening of the condition leading to infection and/or loss of tissue.

3. This device contains solid silicone elastomers. This device does not contain silicone gel. The risks and benefits of implanting this device in patients with documented sensitivity to silicone should be carefully considered.

4. Surgical, physical, psychological, or mechanical complications, if they occur, may necessitate revision or removal of the prosthesis. Removal of the device without timely reimplantation of a new device may complicate subsequent reimplantation. The timing of reimplantation should be determined by the treating physician based on the patient's medical condition and history.

Precautions

Patient Related Precautions

1. Patient selection requires thorough preoperative consultation and evaluation by the physician.

2. Patients should be counseled in order to have a realistic expectation of the physical, psychological, and functional outcome of the implantation of an Acticon™ Neosphincter. Although the prosthesis is designed to restore bowel control some patients continue to have a degree of incontinence after this procedure.

3. Patients may experience pain when the device is activated in the postoperative period and during periods of initial use. Cases of chronic pain associated with the device have been reported. Pain with a severity or duration beyond that which is expected may require medical or surgical intervention. Patients should be counseled on expected postoperative pain including severity and duration.

4. Tissue fibrosis or previous surgery in the area of the implant may preclude implantation of an occlusive cuff at the anal canal.

5. Acute bowel disorders, e.g. diarrhea or constipation, can interfere with proper functioning of the device and may require the use of external pads or manipulations to assist defecation.

6. Any progressively degenerative disease, e.g. multiple sclerosis, may limit the future usefulness of the implanted prosthesis as a treatment of the patient's fecal incontinence.

7. Adequate manual dexterity, strength, and motivation are required for proper use of the device.

8. Trauma or injury to the pelvic, perineal or abdominal areas, such as impact injuries associated with sports, can result in damage to the implanted device and/or surrounding tissues. This damage may result in the malfunction of the device and may necessitate surgical correction including replacement of the prosthesis. The physician should advise patients of these possibilities and warn them to avoid trauma to these areas.

9. If radiopaque solution is used instead of sterile isotonic saline to fill the device, ensure the patient is not allergic to the radiopaque solution.

10. Receptive anal intercourse may damage the occlusive cuff and is not recommended for patients implanted with this prosthesis.

11. Vaginal delivery of children may interfere with future proper functioning of the occlusive cuff. Patients should be made aware of the need to discuss the presence of the Acticon device with their doctors should they become pregnant. A cesarean delivery may be recommended in order to avoid damage to the device.

12. No safety or effectiveness data exists for patients with a history of inflammatory bowel disease or pelvic radiation. The potential for increased risk of erosion in these patients is unknown.

Surgery Related Precautions

1. Improper cuff sizing, improper balloon selection, or other causes such as surgical trauma, poor tissue viability, and concomitant medical procedures, may result in tissue erosion, migration of components, or continued incontinence.

2. Component migration can occur if the cuff is sized improperly, if the pump or balloon is not positioned correctly, or if the tubing lengths are incorrect. Migration can result in pain, complications, device malfunction and surgical revision.

3. Unsuccessful outcomes may result from improper surgical technique, anatomical misplacement of components, improper sizing and/or filling of components.

4. Although reinforced tubing has been designed to be more resistant to tubing kinks, tubing kinks may still result from tailoring the connecting tubing to an improper length during the implant procedure.

Device Related Precautions

1. This device is subject to wear and eventual failure over time. It is not possible to predict how long the implanted prosthesis will function in a particular patient. The device should not be considered a lifetime implant.

2. If the deactivation valve is closed when the cuff is inflated, fluid cannot transfer from the cuff to the balloon and sustained fecal obstruction may arise as a result:

    a) In the event of large pressures within the bowel, automatic pressure relief that normally occurs with the device would be prevented. Cycling the device can relieve the fecal obstruction.

    b) Cycling the device may be difficult if deactivation occurs when the pump bulb is deflated. If unable to cycle the prosthesis, squeezing the sides adjacent to the deactivation button will allow fluid to fill the pump bulb and then the pump can be cycled normally.

    c) Release of the deactivation valve may require greater pressure than that used to cycle the device.

3. Use caution when passing any instrument through the anal canal. For certain procedures, e.g., anal ultrasound or colonoscopy, first deflate the cuff then deactivate the device prior to passing any instrument through the anal canal.

4. System pressure changes may occur over time. This may result in changes in continence status. To increase system pressure, fluid may be added to the device through the septum port.

V. ADVERSE EVENTS OF THE DEVICE ON HEALTH

Discussion of adverse events is based on 115 patients implanted with the Acticon™ Neosphincter in a multi-center, prospective study which evaluated the safety and effectiveness of the device in patients with severe fecal incontinence. A total of 456 adverse events were reported during the clinical trial, 395 (86.6%) of which were considered to be device-related or potentially device-related. One hundred and two (102) of the 115 patients enrolled (88.7%) experienced at least one device-related adverse event. Of these 395 device-related events, 358 (91%) were resolved by the conclusion of the clinical trial. With respect to severity:

- 191 (48%) of the events were rated mild;
- 127 (32%) moderate;
- 55(14%) severe; and
- 22 (6%) were not rated.

With respect to the general modalities of treatment required to address the adverse events:

- 17% required no intevention;
- 57% required medication or a non-invasive intervention; and
- 36% required surgical intervention.

Some of these adverse events may have required both a surgical and a non-surgical intervention to resolve.

Among the 142 surgical interventions were 81 device revision procedures during which part or all of the originally implanted prosthesis was (were) repositioned, replaced, or removed. Fifty-six patients (56) required at least one device revision as a result of adverse events. Thirty-four (34) patients required total device explantation prior to the conclusion of the study.

A summary of the adverse events recorded during the study along with their frequency and method(s) of intervention are depicted in Table 1. Of note, patients may have had more than one type of event or more than one event of the same type. In addition, there may have been more than one type of intervention for each event and patients may have had multiple events treated with the same intervention.

Table 1: Adverse Events and Methods of Intervention for Acticon Neosphincter Study

Adverse Event Type	Number and (%) of Patients	Number of Events	Methods of Intervention			
			None Required	Medication	Surgery	Other[1]
Pain/Discomfort	37 (32.2)	44	15	15	8	14
Infection	36 (31.3)	41	0	16	33	3
Erosion	24 (20.9)	28	0	3	27	2
Recurring fecal incontinence	22 (19.1)	29	2	3	13	11
Constipation	22 (19.1)	33	2	26	2	7
Impaction	21 (18.3)	27	2	7	3	17
Surgical injury	15 (13.0)	15	2	0	11	1
Wound problems	12 (10.4)	13	7	2	1	3
Mechanical malfunction	12 (10.4)	15	1	0	13	1
Wound separation	10 (8.7)	10	4	4	1	2
Difficult evacuation	10 (8.7)	13	1	5	1	8
Rectal bleeding	9 (7.8)	9	5	1	2	1
Edema	9 (7.8)	10	3	3	4	2
Erythema	9 (7.8)	10	3	6	1	2
Fever	7 (6.1)	7	0	6	1	0
Anorectal condition	7 (6.1)	8	1	0	1	6
Device migration	7 (6.1)	9	1	0	7	0
Device Fit	6 (5.2)	6	2	1	3	1
Device Function	6 (5.2)	7	0	0	0	7
Wound drainage	6 (5.2)	7	1	2	1	3
Gastrointestinal condition	5 (4.3)	6	1	1	2	2
Diarrhea	5 (4.3)	7	2	1	0	4
Ecchymosis	4 (3.5)	4	3	0	0	1
Malposition	4 (3.5)	4	1	0	3	0
Device operation difficulty	3 (2.6)	3	0	0	0	3
Other [2]	27 (23.5)	20	7	3	1	9
Totals		**395**	**67**	**106**	**142**	**117**

[1]Other interventions reported included: fluid added to pump via septum (15), enemas (14), deactivation of device (13), patient education (11), hospitalization (9). There were 18 reports of an unspecified "other" intervention.

[2]Other adverse events included abscess (2), difficult device activation (2), hematoma (2), intraoperative bleeding (2), seroma, urinary tract infection, acute renal failure, ankle pain, chest rash, decreased perianal sensation, hip ulcer, hyperglycemia secondary to infection, mild pancreatitis, night sweats, osteomyelitis, patient dissatisfaction, patient falling, couldn't pump device, device locked, post-stoma takedown paralytic ileus, morphine reaction, respiratory distress, severe acute esophagitis, urinary retention (2), vaginal rash and weakness.

VI. DEVICE DESCRIPTION AND OPERATION

The Acticon™ Neosphincter is an implantable, fluid filled, solid silicone elastomer device used to treat severe fecal incontinence. The Acticon™ Neosphincter consists of three interconnected components: an occlusive cuff, a pressure-regulating balloon and a control pump with a septum. The components are connected with color-coated, kink-

resistant silicone tubing. The occlusive cuff is available in multiple different sizes (widths of 2.0 and 2.9cm and lengths ranging from 8.0-14.0cm). The proper size is determined intra-operatively by the use of a cuff sizer. The control pump is 1.2cm by 3.6cm and contains the valves needed to transfer fluid to and from the cuff as well as a deactivation button, squeeze bulb, and septum port for adding fluid post-operatively. The pressure-regulating balloon is available in 4 different pressure ranges (81-120cm H2O). Only the shell wall thickness differs in the available balloon ranges. It is 4.1cm in diameter when filled with 40cc of fluid and controls the amount of pressure exerted on the anal canal by the occlusive cuff. AMS Quick Connect™ Sutureless Window Connectors and/or Suture-Tie Connectors are used to connect the tubing components and are included in an accessory kit. In addition, the accessory kit contains disposable blunt needles, the disposable cuff sizer, and a locking ring holder. An Acticon-specific tubing passer, used to route the tubing of the components through the appropriate tissue planes during implantation, is also required during the surgical procedure. A Quick Connect™ assembly tool is available separately if the Quick Connect™ Sutureless Window Connector System is to be used. Figure 1 shows the device and its components.

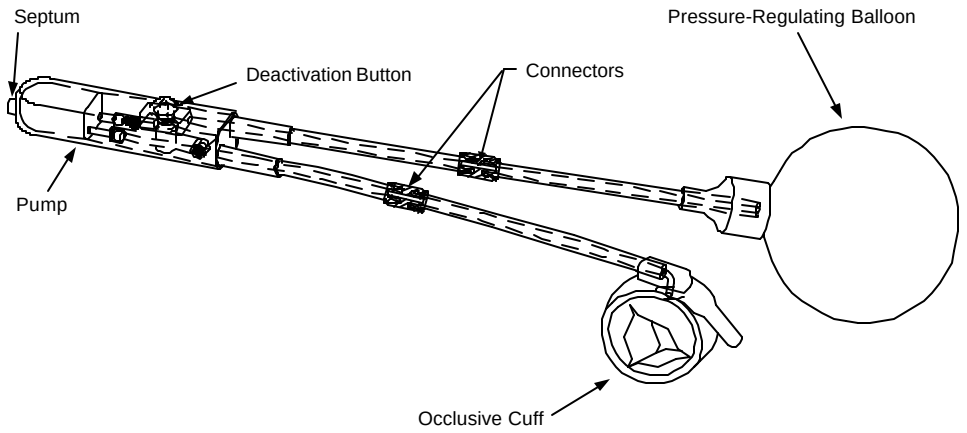


Figure 1
The AMS Acticon™ Neosphincter

The device simulates normal anal sphincter function by allowing the anal canal to open at the control of the patient. The occlusive cuff is surgically implanted around a segment of the anal canal. The device maintains continence in the patient by using the pressure of the fluid filled cuff to occlude the anal canal circumferentially. To evacuate the bowel, the patient squeezes and releases the pump mechanism, located in the labium or scrotum, several times to move fluid from the cuff to the pressure-regulating balloon implanted in the abdomen. This movement of fluid empties and collapses the cuff, resulting in the release of the compressive force around the anal canal. This allows the patient to defecate. Residual pressure within the regulating balloon allows fluid to flow back into the cuff, automatically re-pressurizing the occlusive cuff within a few minutes. A patient may need to squeeze the pump more than once to complete a bowel movement.

VII. ALTERNATIVE PRACTICES AND TREATMENTS

Fecal incontinence is the involuntary loss of flatus, liquid, or solid stool and presents in a range of severity. Fecal incontinence is a condition that can have distressing effects on a person's working life, social life, and emotional well-being. Individuals who suffer from the condition often alter their lifestyle to minimize the likelihood of bowel accidents in public places. Fecal incontinence may result from a variety of disease processes including injury to the anal sphincter from obstetrical or surgical procedures, trauma, rectal prolapse, neurological diseases or impairment, intestinal infection, fecal impaction, and collagen vascular diseases.

The vast majority of cases of fecal incontinence are mild to moderate and can be managed with medical interventions such as pharmacological therapy and dietary modifications. In one subgroup of patients with retained rectal sensation and the ability to voluntarily contract the external anal sphincter, biofeedback may be successful in up to 90% of those treated. Surgical repairs may benefit certain patients including those with sphincter defects and rectal prolapse. Success rates for these procedures may approach 70-90%.

For individuals with severe fecal incontinence who have failed medical interventions and/or are not candidates for biofeedback or surgical repair, the choices are limited.

Adynamic muscle transposition, an alternative surgical procedure, may be used in patients where the anal sphincter is either denervated or anatomically absent. It involves the transposition of a muscle, usually the gracilis or gluteus maximus, to create a barrier to the passage of stool. Success rates for this type of surgery vary greatly. Finally, some patients are faced with a choice of permanent ostomy, a surgically created passage to allow bodily wastes to be expelled from the body through the abdominal wall.

VIII. MARKETING HISTORY

Foreign Market Introduction

A CE-mark for the Acticon™ was received in May of 1996. Limited marketing of the Acticon™ Neosphincter in select European countries and Australia began in July of 1996. In 1998 the device was introduced in other markets including Brazil, Canada, China, Europe, and Taiwan. The Acticon™ Neosphincter has not been withdrawn from marketing for any reason related to lack of safety or effectiveness.

Domestic Market Introduction

Humanitarian Device Exemption approval was received in September of 1999. In accordance with HDE approval orders, including the need for IRB approval, marketing of the Acticon™ Neosphincter at select centers in the United States began in October 1999.

IX. SUMMARY OF PRECLINICAL STUDIES

Materials Safety and Toxicology Testing
The safety of the materials used in the Acticon™ Neosphincter were evaluated through a testing program that included chemical analysis of exhaustive extracts, infrared spectral analysis of surfaces having direct tissue contact, and a series of *in vitro* and *in vivo* biological studies. All biological non-clinical laboratory studies were conducted in compliance with the Good Laboratory Practice Regulations.

Chemical Analysis of Extractives
Testing conducted on two other marketed devices manufactured by AMS, the AMS Model 800 Artificial Urinary Sphincter (AUS) and the AMS Dynaflex inflatable penile prosthesis were used to support safety of the Acticon™ Neosphincter. These devices use the identical materials and the design of the AUS is almost identical to the Acticon™ Neosphincter. Extractive analysis identified compounds that may leach from the Acticon™ Neosphincter and quantified the potential exposure to each extractive. These included polydimethylsiloxanes of varying molecular weights (296 to >150,000 daltons), water soluble silica (silicic acid), formaldehyde, and traces of platinum and tin catalysts. For each extractable compound known to produce some toxic or irritant effect(s) the total potential exposure from an Acticon™ Neosphincter was shown to be well below the exposures required to produce any observed effect based on published toxicity data for each extractive. Exposure to leachable components at the concentrations present in the Acticon™ Neosphincter was determined not to be a significant health risk for patients.

Infrared Spectra Surface Analysis
To document the principle chemical composition for each device component which could have direct tissue contact, infrared spectra of the outer device surfaces were collected using attenuated total reflectance Fourier transform infrared spectroscopy. Testing showed that only polydimethylsiloxane has direct tissue contact. No other materials or unusual spectral features were detected.

Biological Safety Tests
Finished products were subject to the complete spectrum of biological tests cited in the "Guidance for Manufacturers of Silicone Devices Affected by Withdrawal of Dow Corning Silastic Materials (July 6, 1993)." This included tests for *in vitro* cytotoxicity, acute systemic toxicity, intracutaneous irritation, sensitization, direct tissue contact (intramuscular implantation for 14 and 90 days) and three genetic toxicity tests.

Studies were also conducted in which substantial amounts of ground silicone elastomer were implanted subcutaneously in Sprague Dawley rats. The effects of the implanted material on the host system was evaluated. The tests included an acute pharmacokinetic study (distribution and excretion of silicones), testing for effects on the immunological system (immunomodulation and adjuvanticity), and studies for sub-chronic and chronic toxicity, reproductive effects, and oncogenicity.

Test results indicate that the materials used in the Acticon™ Neosphincter do not produce localized or systemic toxic effects when implanted.

Mechanical Testing

A risk analysis, including a failure modes and effects analysis (FMEA), was used to identify safety and reliability attributes applicable to the Acticon™ Neosphincter or its components. Bench testing was performed to characterize the device components, attributes, and functions. All bench testing was performed on finished, sterilized devices or components.

Performance Characteristics Testing

Performance characteristics of the device were evaluated by testing samples for the following performance characteristics:

- Squeeze force versus fluid displacement
- Fluid displacement per pump stroke
- Prevention of spontaneous inflation or deflation
- Pump output pressure produced by pump squeeze force
- Pump bulb refill time
- Pump deactivation force and activation pressure
- Pump valve leakage and maximum back pressure
- Tubing kink resistance
- Balloon capacity
- Cuff expansion and maximum pressure

These tests demonstrated that the performance of the device and its components meet the specifications and clinical requirements of the device. Test results also indicated that device performance was not affected by the sterilization method or accelerated aging.

Reliability Testing

Device reliability attributes were evaluated in bench testing by subjecting samples to representative *in vivo* conditions, where possible, and to a number of uses likely to exceed the number of uses over the estimated life of the device. The following reliability testing was performed:

- Cuff deflation/inflation cycling
- Pump cycling
- Balloon inflation/deflation cycling
- Pump cycling and septum access
- Cuff fold wear resistance life cycling
- Prosthesis adhesive bond reliability

Reliability testing demonstrated that the device and its components exceeded the simulated use conditions equivalent to 10 years.

Component Strength Testing
Device strength attributes were evaluated by subjecting test samples under representative *in vivo* conditions, where possible, and for a number of uses likely to exceed the number of uses over the estimated life of the prosthesis for the following strength attribute analysis:

- Cuff maximum pressure and expansion
- Cuff leakage or unbuckling under pressure
- Connector strength
- Tubing burst/leak pressure
- Connector/component leak pressure
- Subassembly bond strength
- Prosthesis material strength

Component strength testing demonstrated acceptable prosthesis or component performance over the estimated use conditions.

Shelf Life Testing
Shelf life was determined to be equivalent to the shelf life of the AMS inflatable penile prostheses products (700, Ultrex, CX, Ambicor) and the AMS 800 artificial urinary sphincter. The three product lines use the same materials for packaging. An accelerated aging study was performed on the package configuration and showed the packaging would provide physical protection and a sterile barrier for a 5-year shelf life with a 2-year safety margin. The Acticon™ Neosphinter is labeled with a "use before date" which is 5 years from the date of manufacture.

Sterilization
The components of the Acticon™ Neosphincter Prosthesis are sterilized using either steam or ethylene oxide. The sterilization protocols are adequate. The identical methods for sterilization are used with the American Medical Systems Artificial Urinary Sphincter.

The pressure regulating balloon is sterilized at a contract sterilization facility, using ethylene oxide, to a sterility assurance level of 10^{-6}. American Medical Systems uses steam to sterilize the cuff and pump at their facility in Minnetonka, Minneasota, to a sterility assurance level of 10^{-6}.

Two components of the system the AMS Quick Connect Assembly Tool and AMS Tubing Passers are shipped to the user nonsterile. The AMS Quick Connect Assembly Tool and Tubing Passers are reusable components used during surgical placement of the system. They are shipped to the user nonsterile in steam sterilization packages ready for hospital sterilization.

X. **SUMMARY OF CLINICAL STUDIES**

Two clinical studies conducted in the United States by American Medical Systems, are described in the PMA to support the safety and effectiveness of the Acticon™ Neosphincter. The first study (IDE #G880037) began in August 1988 and was closed in April 1995. The second study (IDE #G960116) started enrolling subjects in February 1997 and was closed in December of 1999.

IDE #G880037

This study was a multi-center, prospective pilot study of the Artificial Bowel Sphincter (ABS), an earlier version of the Acticon™ Neosphincter which was adapted from the AMS 800 Urinary Sphincter. Patients selected for the study demonstrated fecal incontinence unresponsive or unlikely to respond to accepted medical or surgical alternatives. The objectives of this study were to:

- demonstrate that the device could be implanted without adverse sequelae;
- demonstrate that the device provided an acceptable level of continence;
- demonstrate that the anticipated adverse events had a low incidence and could be managed without long-term sequelae; and
- demonstrate that there were no unanticipated adverse responses associated with the device.

A total of 21 patients (11 females and 10 males) ranging in age from 15-68 years were enrolled at 3 different sites for this study. The etiologies of incontinence are provided in Table 2.

Table 2: Etiology of Incontinence (IDE #G880037)

Etiology of Incontinence	**Number of Patients**	**Percent**
Major Trauma	6	28.6
Birthing Injury	5	23.8
Imperforate Anus	3	14.2
Spinal Cord Tumor	2	9.5
Laminectomies	2	9.5
Spina Bifida	1	4.8
Myasthenia Gravis	1	4.8
Prolapse Intervertebral Disc	1	4.8
Total Patients	21	100

Adverse events that occurred during the pilot study included:

- infection (5 patients);
- mechanical malfunction (5 patients with 2 patients having multiple problems); and
- pain (2 patients).

Device revisions which included repositioning, replacing or removing specific components or the entire device, were required in 9 of the 21 patients (43%) including all 5 with mechanical malfunction and 4 of the 5 patients with infection. One case of

infection resolved with antibiotics alone. Five of the 21 patients (24%) required permanent device explantation (2 of the 5 patients with malfunction and 3 of the 5 with infection).

Effectiveness outcomes were based on manometry testing and continence diaries. Patient follow-up ranged from 6 to 76 months. The 16 patients who did not require device explantation were considered in the analysis of effectiveness. The investigators reported that 64% (10/16) of these patients achieved complete continence to liquid and solid stool. An additional 18% (3/16) achieved continence to solid stool but experienced occasional leakage of liquid stool. When all patients enrolled in the study are taken into account on an intent to treat basis, 62% (13/21) demonstrated either improvement or resolution of their fecal incontinence.

Study Conclusions
Based on the results of this study (IDE #G880037) the sponsor conducted additional product development which included modifications to the device in preparation for a modified and expanded pivotal clinical trial. Compared to the ABS, the newer Acticon™ Neosphincter was designed with:

- a longer reinforced cuff;
- a larger (40cc) pressure regulating balloon; and
- a septum as part of the control pump to add fluid to the system post-operatively.

IDE #G960116

Study Design
This second, larger pivotal study was a multi-center, prospective, non-randomized trial in which each subject served as his or her own control. Patients at least 18 years of age with severe incontinence without regard to etiology were considered for implantation of the device. Severe fecal incontinence, as defined in the protocol, was the involuntary loss of liquid or solid stool on a weekly or more frequent basis. The main objectives of the study were to:

- demonstrate that the Acticon™ Neosphincter could be surgically implanted without serious adverse sequelae;
- demonstrate that the Acticon™ Neosphincter provided an acceptable level of continence as determined through the use of the Fecal Incontinence Scoring System (FISS) Questionnaire; and
- report the adverse events associated with the implantation of the Acticon™ Neosphincter and to demonstrate that the events could be managed without serious sequelae.

Patient Selection

Patient Inclusion Criteria

1. Patient had fecal incontinence for at least 6 months.
2. Patient failed at least one non-surgical treatment for incontinence.
3. Patient had a FISS incontinence score of at least 88.
4. Patient was at least 18 years of age.
5. Patient was an acceptable risk for surgery and anesthesia.
6. Patient was willing to give informed consent.
7. Patient was willing to return for follow-up visits.
8. Patient was able to understand and complete questionnaires.
9. Patient's life expectancy was greater than 2 years.
10. Patient had sufficient dexterity and mental capacity to operate the device.

Patient Exclusion Criteria

1. Patient had a FISS score less than 88.
2. Patient had irritable bowel syndrome as their only cause of incontinence.
3. Patient had inflammatory bowel disease.
4. Patient had active pelvis sepsis.
5. Patient was pregnant.
6. Patient had a history of extensive pelvic radiation that would compromise the anal canal.
7. Patient had a scarred and fragile perineum.
8. Patient had engaged in anal receptive intercourse.
9. Patient had enrolled in another study involving investigational products.

Patient Demographics and Etiology

A total of 115 patients were enrolled at 19 different sites in the United States (13), Canada (3), France (2), and Spain(1). This included 86 females (75%) and 29 males (25%). The average age at enrollment for females was 53, males 36 (p=0.0001, females versus males), and overall, 47. Caucasians comprised 80% of those enrolled, Hispanics 4%, African-Americans 3%, and Asians 2%. The races of 11 European patients were not recorded. The etiologies of incontinence are shown in Table 3.

TABLE 3- Distribution of Patients by Etiology

Etiology of Fecal Incontinence	Number of Patients	Percent (%)
Obstetric Trauma	34	29.57
Neurological	23	20.00
Congenital Abnormality	23	20.00
Anorectal Trauma	21	18.26
Other[1]	14	12.17
Total Patients	**115**	**100**

[1]Other includes: rectal prolapse (3), idiopathic (3), radiation (1), surgical (3), scleroderma (1), traumatic defecation (1), musculoskeletal (1), and anal canal squamous cell carcinoma (1)

Pre-Implant Procedures and Treatment

All patients had undergone, and failed, at least one traditional non-surgical treatment for fecal incontinence prior to receiving the Acticon™ Neosphincter. In addition, many of the patients had also undergone a surgical procedure prior to implantation. These therapies are shown in Table 4.

TABLE 4
Distribution of Patients by Previous Treatment for Fecal Incontinence

Type of Previous Treatment[1]	Total Patients[1]	Percent (%)
Management:		
Bowel Management	83	72.2
Biofeedback	25	21.7
Surgical Treatment:		
Sphincteroplasty	38	33.0
Stoma	30	26.1
Rectal Prolapse Repair	12	10.4
Gracilis Muscle Transposition (stimulated)	5	4.3
Gracilis Muscle Transposition (unstimulated)	2	1.7
Postanal Repair	2	1.7
Other[2]	29	25.2

[1] Patients with multiple types of treatments were counted more than once. Therefore, the total number of patients reported for all etiologies is greater than the actual number of patients enrolled. Percentages have been calculated based on the actual number of patients enrolled and therefore also add up to more than 100%. Percentages are percentage of patients having had the specific type of treatment. However, some patients had more that one procedure of the same type, and these are captured under the "other" category. [2] Other includes: Second sphincteroplasty (10), silastic sling (3), repair of imperforate anus (4), revised colostomy (3), repeated rectal prolapse repair (2), repair neosphincter and second gracilis muscle wrap, posterior sagioplasty/vaginal anoplasty, abdominal exploratory/rectopexy and levatorplasty, posterior colporrhaphy/repair perineal body, 4-V advancement flap, neorectum, vaginal and anal reconstruction.

Follow-up

Two weeks after implantation, patients were seen for evaluation of the surgical wound. The patients returned to their physician's office 6-8 weeks after implantation for activation of the device. Those patients with pre-existing ostomies underwent stoma take-down. Patients were then followed at 6 and 12 months. At the 6-month follow-up patients underwent a history/physical examination and anorectal manometry. In addition, the FISS and Fecal Incontinence quality of life questionnaires were completed by the patient. At 12 months the patients had these same evaluations as well as an endoanal ultrasound and the Health Status Quality of Life questionnaire.

Patient Accountability

One hundred and fifteen (115) patients were enrolled in the study and 112 underwent device implantation. For one of the three patients who were enrolled but not implanted with the device, a large enough cuff was not available. A second patient was found to have megarectum with stool impaction at the time of surgery and was not implanted. A third patient experienced perforation at the time of surgery and elected not to continue in the study. Table 5 shows the follow-up compliance for the 112 patients implanted with the device.

TABLE 5 -Follow-up Compliance

Patient Status	Activation	6 Months	1 Year
Follow-up performed	98	73	69
Due for follow-up	0	0	1
Missed follow-up	1	6	5
Not eligible for follow-up	0	0	0
Explanted	13	31	34
Deceased	0	0	0
Lost to follow-up	0	2	3
Total Patients	**112**	**112**	**112**

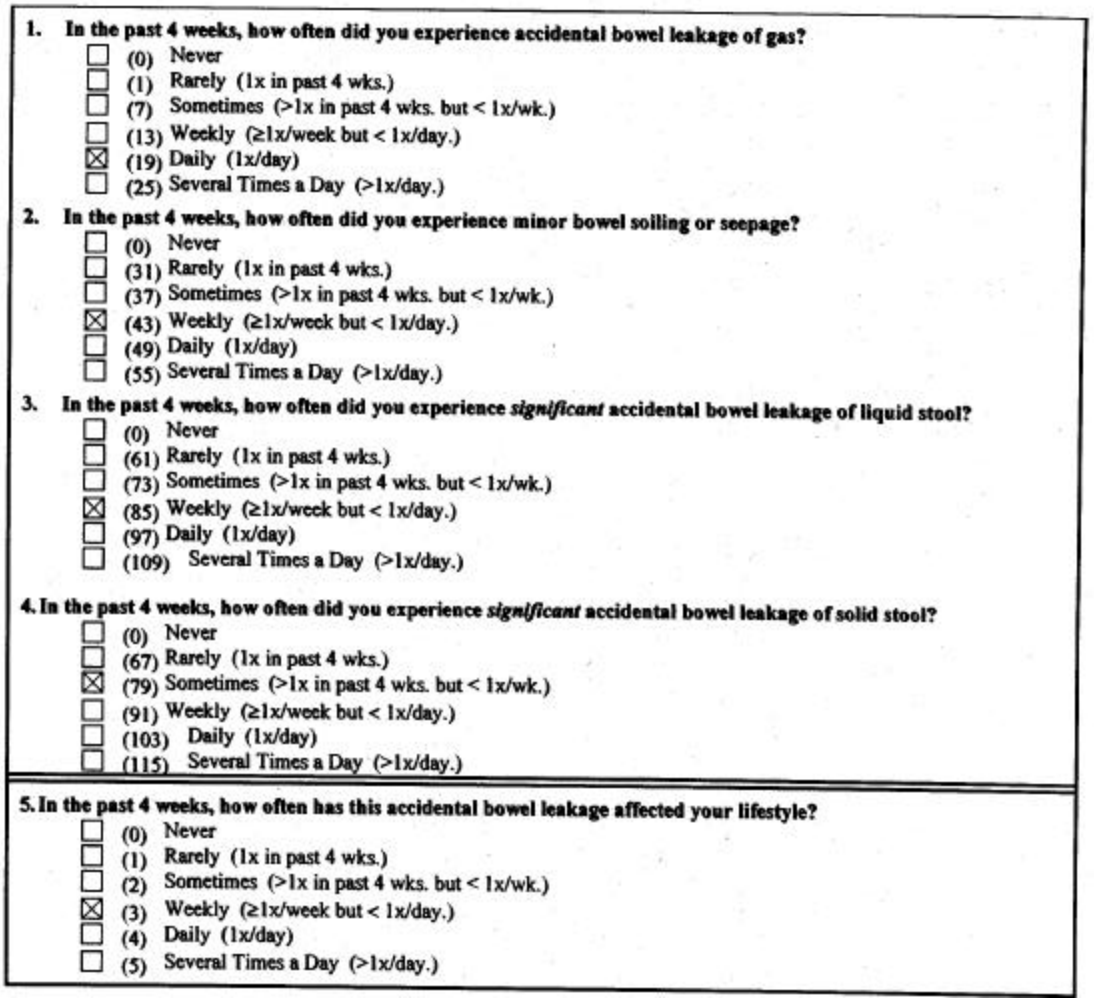
Endpoints

Change in incontinence symptoms after one year of treatment as determined by the Fecal Incontinence Scoring System (FISS) was used as the study's primary effectiveness endpoint. Device effectiveness was assessed by analyzing the difference between the pre-implant FISS score and the score at 12 months post-implantation. This scale was developed in part by the sponsor and has been validated by Vaizey *et al* (*Gut* 1999; 44:77-80). The FISS is a self-administered, 5-item questionnaire which assesses the frequency and severity of the patient's incontinence symptoms. Four questions assess how often in the proceeding 4 weeks a patient has experienced leakage of

- gas;
- seepage/soiling;
- liquid stool; and
- solid stool.

The fifth question assesses the effect of accidental bowel leakage on the patient's lifestyle. Each possible response had a unique score assigned to it. A sample of the FISS questionnaire is shown in Figure 2.

Figure 2. Fecal Incontinence Scoring System Questionnaire



1. In the past 4 weeks, how often did you experience accidental bowel leakage of gas?

- ☐ (0) Never
- ☐ (1) Rarely (1x in past 4 wks.)
- ☐ (7) Sometimes (>1x in past 4 wks. but < 1x/wk.)
- ☐ (13) Weekly (≥1x/week but < 1x/day.)
- ☒ (19) Daily (1x/day)
- ☐ (25) Several Times a Day (>1x/day.)

2. In the past 4 weeks, how often did you experience minor bowel soiling or seepage?

- ☐ (0) Never
- ☐ (31) Rarely (1x in past 4 wks.)
- ☐ (37) Sometimes (>1x in past 4 wks. but < 1x/wk.)
- ☒ (43) Weekly (≥1x/week but < 1x/day.)
- ☐ (49) Daily (1x/day)
- ☐ (55) Several Times a Day (>1x/day.)

3. In the past 4 weeks, how often did you experience *significant* accidental bowel leakage of liquid stool?

- ☐ (0) Never
- ☐ (61) Rarely (1x in past 4 wks.)
- ☐ (73) Sometimes (>1x in past 4 wks. but < 1x/wk.)
- ☒ (85) Weekly (≥1x/week but < 1x/day.)
- ☐ (97) Daily (1x/day)
- ☐ (109) Several Times a Day (>1x/day.)

4. In the past 4 weeks, how often did you experience *significant* accidental bowel leakage of solid stool?

- ☐ (0) Never
- ☐ (67) Rarely (1x in past 4 wks.)
- ☒ (79) Sometimes (>1x in past 4 wks. but < 1x/wk.)
- ☐ (91) Weekly (≥1x/week but < 1x/day.)
- ☐ (103) Daily (1x/day)
- ☐ (115) Several Times a Day (>1x/day.)

5. In the past 4 weeks, how often has this accidental bowel leakage affected your lifestyle?

- ☐ (0) Never
- ☐ (1) Rarely (1x in past 4 wks.)
- ☐ (2) Sometimes (>1x in past 4 wks. but < 1x/wk.)
- ☒ (3) Weekly (≥1x/week but < 1x/day.)
- ☐ (4) Daily (1x/day)
- ☐ (5) Several Times a Day (>1x/day.)

The final FISS score is obtained by taking the highest score from the first 4 questions and adding the score from the 5th question. In the sample questionnaire in Figure 2, a total score of 88 would be recorded for that patient. The correlation of FISS scores to bowel activity is shown in Table 6.

Table 6: Fecal Incontinence (FI) Score Definitions

FI Value	Definition
0-60	Continent to solid and liquids
61-72	Incontinent < monthly
73-84	Incontinent > monthly
85-96	Incontinent >weekly
97-108	Incontinent daily
109-120	Incontinent >daily

A patient was considered to have a clinically successful outcome at the one-year follow-up point if he or she had a score reduction of $\geq$ 24 points compared to baseline (pre-implant).

Secondary endpoints were also evaluated pre and 12 months post-implantation to assess effectiveness, safety and impact on patient quality of life. These endpoints included:

- all adverse device events;
- mean resting sphincter pressures as determined by anorectal manometry; and
- alterations in quality of life as measured by two separate questionnaires, one addressing specific incontinence issues (Fecal Incontinence Quality of Life) and the other general health (Health Status Questionnaire).

Effectiveness

Primary Effectiveness Endpoint: Fecal Incontinence Scoring System (FISS)
Of the 115 patients enrolled in the study, pre-implant FISS scores were not attainable in 14 patients with a pre-existing stoma. For the remaining 101 patients, the mean score prior to implantation was 106 (range 71-120). Thirty-eight (38) patients (33%) scored in the most severe category (score 109-120) prior to implantation with 23 (20%) having the maximal score of 120. Thirty-five patients (30%) had pre-implant scores of 97-108, and the remaining patients had either scores of 96 or less (28 patients).

For 63 patients, FISS scores had been collected at both pre-implantation and at the 12-month follow-up. The mean 12-month score for this set of patients was 48 compared to 105 at baseline ($p<0.0001$), representing an average reduction in score of 57 points. Of these 63 patients, 54 (85.7%) had a reduction in FISS score of $\geq$24 points at the 12 month follow-up and were therefore considered to have had a clinically successful outcome. At the 12-month follow-up, females had a greater drop in FISS score (58 points) compared to males (50 points). This difference was statistically significant ($p<0.05$), but the clinical significance is uncertain as the number of males enrolled was small and both groups on average showed reductions of more than twice that required to define clinical success. No other significant differences were noted among other subgroups including age and etiology of incontinence. In addition to these 63 patients, 6 patients with pre-existing stomas completed 12 months of follow-up bringing the total of patients with 12-month FISS scores to 69. Of these 69 patients:

- 7 (10%) had achieved total continence (score of zero);
- 11 (16%) were incontinent to gas only; and
- 29 (43%) reported seepage or rare incontinence to liquid or solid stool

Intent to Treat Analysis
Six patients with a pre-existing stoma completed follow-up and had 12-month FISS scores available. To be included in an intent to treat analysis, these 6 patients had a pre-implant FISS score of 106 (the average for the 101 non-stoma patients) assigned to them. Using this assumption, 5 of these 6 stoma patients had a successful outcome at 12 months as defined by a $\geq$24-point drop in FISS score.

A total of 34 patients had the Acticon ™ device entirely explanted before reaching their 12-month follow-up and were considered treatment failures in the intent to treat analysis.

In addition, the three patients with aborted implantation, the 6 patients with missing 12-month data and the 3 patients lost to follow-up were also considered treatment failures.

By an intent to treat analysis which accounts for all enrolled patients, the clinical success rate for the Acticon™ Neosphincter based on 12-month FISS scores was 51.3% (59 of 115).

Secondary Effectiveness Endpoint: Anorectal Manometry.
Mean anal sphincter resting pressures were evaluated by anorectal manometry prior to implantation and at the 6 and 12-month follow-up visits. Results of these manometry studies are shown in Table 7.

TABLE 7 -Anorectal Manometry Resting Pressures (mmHg)

	Pre-Implant (n=106)	Activation (n=73)	6 Month Post Activation (n=61)	12 Month Post Activation (n=53)
Mean	26	47	46	45
Minimum	0	8	12	14
Maximum	70	78	80	77
Standard Deviation	15	17	16	16

There was a significant difference ($p<0.0001$) in mean resting pressures between pre-implant and 12-month follow-up. In addition, the data suggested a statistically significant correlation between lower FISS scores and higher mean resting pressures at 12 months (correlation = -0.38, $p = 0.0039$).

Secondary Effectiveness Endpoint: Fecal Incontinence QOL (FIQOL) Questionnaire.
The Fecal Incontinence Quality of Life Questionnaire is a psychometric evaluation which assesses the impact of accidental bowel leakage on a variety of activities and feelings. The 39-item questionnaire was self-administered to the patients prior to implantation and at the 6 and 12-month follow-up visits. For each feeling or activity, the patients were asked to respond with one of the following 5 choices:

- Most of the Time OR Strongly agree;
- Some of the Time OR Somewhat Agree;
- A Little of the Time OR Somewhat Disagree;
- None of the Time OR Strongly Disagree; or
- Does Not Apply

Sixty-seven (67) patients completed the FIQOL questionnaire at their 12 month follow-up visit. The percentage of patients responding “Most of the time” or “Strongly agree” at baseline and at the 12 month follow-up for the most common feelings or activities are shown in Table 8.

Table 8. Fecal Incontinence Quality of Life

Feeling or Activity	Pre-Implant (n=113)	12 months (n=67)
Feel I have no control over bowels	89%	9%
Worry about accidents	86%	22%
Alter activities to be near bathroom	81%	33%
Worry about being embarrassed	80%	25%
Bowel accidents are always on my mind	78%	25%
Use pads	77%	39%
Worry about others smelling stool	76%	19%
Locate bathrooms when someplace new	76%	34%
My life is more difficult	70%	15%
Afraid to wear light colored clothing	69%	24%
Cannot do things I want to	68%	16%
Feel ashamed	66%	18%
Plan schedule around bowels	65%	21%

Secondary Effectiveness Endpoint: Health Status Questionnaire (HSQ 2.0).
The Health Status Questionnaire (HSQ 2.0) was developed by the Health Outcomes Institute and was self-administered by the patients prior to implantation and at the 6 and 12 month follow-up intervals. This was derived from the MOS-20 questionnaire which was validated as part of the Rand Corporation's Medical Outcomes Study. Three questions regarding depression were added for this study. The questionnaire consists of 8 scales/domains related to general well-being. Each scale produced possible scores from zero to 100, with 100 representing ideal functioning. Data was available on 48 patients who had completed an HSQ prior to implantation and at the 12-month follow-up. The mean overall score increased from 457 at baseline to 555 ($p<0.0001$) at 12 months. Of the 8 distinct scales, 6 showed statistically significant improvement at 12 months. These results are summarized in Table 9.

TABLE 9 -Health Status Questionnaire 2.0

Scale	Mean D pre-implant to 12-mos. (n=48)	p-value
Health Perception	9.16	0.0011
Physical Functioning	16.62	<0.0001
Role Limitations/Physical Health	22.02	0.0019
Role Limitations/Emotional Problems	10.34	0.1232
Social Functioning	18.02	<0.0001
Mental Health	13.17	0.0002
Bodily Pain	6.92	0.1610
Energy/Fatigue	7.13	0.0400
Overall HSQ	97.94	<0.0001

Secondary Effectiveness Endpoint: Safety and Adverse Events
No deaths or life-threatening conditions were reported during the clinical trial.

Adverse Events
Table 1 (Adverse Events Of The Device On Health, page 6) lists the device-related adverse events observed during the pivotal clinical study and the methods of intervention which were required. A total of 395 device-related adverse events occurred in 102 patients. These events are discussed in further detail below.

Surgical Injury
Fifteen (15) adverse events were reported to occur at the time of implant surgery. These included:

- perforation to the vagina and/or rectum (12 cases);
- perforation of the bladder (2); and
- separation of deactivation plug from tubing in the subcutaneous tissue (1).

All surgical injuries encountered at the time of the original implant procedure resolved without any long-term sequelae.

Infection
Thirty-six patients (31%) experienced 41 device-related infectious adverse events during the course of the clinical study. Eleven separate infectious events in 8 patients resolved with antibiotics alone. The remaining 30 infectious complications, which occurred in 28 different patients, required surgical device revision to correct (See **Device Revisions** below).

Erosion
Erosion of the Acticon™ Neosphincter device into or through surrounding tissue occurred 28 times in 24 different patients (21% of those enrolled). The more common locations for erosion included:

- cuff eroding to the rectum;
- cuff eroding to the perineum; or
- pump eroding through the skin of the labia or scrotom.

Although not seen during the course of the clinical trial, the possibility for erosion of the pressure-regulating balloon to the bladder or bowel also exists. Twenty-seven of the erosion events required a revision surgery to correct (See **Device Revisions** below).

Change in Bowel Habits
Following implantation with the Acticon™ Neosphincter, 22 patients (19%) experienced difficulty with constipation and 21 patients (18%) experienced at least one episode of fecal impaction. The majority of these adverse events (94% and 89% respectively) improved or were resolved with non-surgical management. In addition, 22 patients (19%) also noted a return or worsening of fecal incontinence after an initial improvement in their symptoms. Most of these patients were managed conservatively as well.

Mechanical Malfunction

Mechanical malfunctions occurred in approximately 10% of patients enrolled in the study and included difficulties with the cuff opening or leaking and pump malfunction. The majority of these occurred early in the course of the study. Ninety-two percent (92%) of these mechanical malfunctions required further surgery to correct.

Migration

Device migrations, mainly involving the control pump, occurred in 6% of patients implanted with the device. Eight-nine percent (89%) of these events required surgical intervention.

Surgical Interventions

A total of 101 surgeries were performed following the initial device implant in 60 patients to resolve 142 specific device-related adverse events. In some cases, multiple adverse events may have been resolved by a single surgery. Of the 101 surgeries, 81 consisted of device revisions.

Device Revisions

A revision was defined as any surgical procedure involving the Acticon™ Neosphincter subsequent to the original implant procedure. During revision, one or more of the device components may have been repositioned, removed, and/or replaced. A total of 81 device revisions were required in 56 of the 112 implanted patients, giving a revision rate of 50%. Of these 56 patients:

- 38 (34% of implanted patients) required 1 revision surgery;
- 14 (13%) required 2 revision surgeries;
- 1 (1%) required 3 revision surgeries; and
- 3 (3%) required 4 revision surgeries

The indications for revision are shown in Table 10. Patients may have had multiple occurrences of the same event type. In addition, more than one reason may have existed for each revision. For example, infection and erosion occurred simultaneously as an indication for revision in 13 cases.

Table 10: Device Revisions from Acticon Neosphincter Clinical Study

Reasons for revision [2]	Number of Events[1]	Number of Patients	% of patients (n=112)
Infection	30	28	25.0
Erosion	27	24	21.4
Malfunction	13	11	9.8
Recurring Incontinence	11	10	8.9
Migration	7	6	5.4
Pain	6	6	5.4
Patient Dissatisfaction	4	4	3.6
Malposition	3	3	2.7
Other[1]	13	13	11.6
Total:	81	56	50.0

[1] Other reasons for revision included replacing previously removed cuff (2), incision open (1), two stage device removal (2), cuff opened (3), cellulitis/erosion of the peritoneal skin (1), improperly sized cuff (1), constipation (2) and ano-urethral communication (1)

Ten patients who underwent one or more revision surgeries prior to the 12 month visit had functional devices at 12 months. Eight (8) of these 10 patients were considered clinical successes by FISS Scores.

Infection and Revision

Twenty-five percent (25%) of patients implanted with the Acticon™ Neosphincter experienced at least one infectious complication which required surgical revision to correct. Of the infectious events which eventually led to a revision procedure, 32% occurred within 30 days, 43% within 60 days, and 54% within 90 days of the original implantation surgery. During the course of the pivotal study, a revised and stringent peri-operative antibiotic regimen was instituted when it was recognized that infectious complications were the leading cause of surgical revisions. Only 2 of the 16 patients (12.5%) who received this regimen developed an infectious complication that required a revision procedure.

Erosion and Revision

Twenty-four implanted patients (21.4%) experienced at least one erosion event and a total of 27 revision surgeries were required to correct the event. The locations of these erosions included:

- Cuff erosion to the rectum (12 cases)
- Cuff erosion to the perineum (10 cases)
- Pump erosion through the skin of the scrotom or labium (4 cases)
- Tubing erosion (1 case)

Device Explantations

An explantation was the surgical removal of the entire prosthesis after the original implantation. A total of 34 patients (30% of those implanted) had the Acticon™ Neosphincter explanted within one year of implantation. Four (4) patients had the device explanted twice. The average time from implantation to device explant in these patients was 4.2 months, however 38% (13/34) occurred prior to the activation follow-up which was scheduled to occur 6-8 weeks after implantation and 91% (31/34) occurred within the first six months. Infection and/or erosion were the indication(s) for device removal in 92% (35/38) of the cases as shown in Table 11.

Table 11:Device Explants from Acticon Neosphincter Clinical Study

Reasons for explant	Number of Events[1]
Infection	12
Infection and erosion	12
Erosion	11
Recurring Incontinence and pain	2
Ano-urethral communication	1
Total Explants	**38**

[1]Patients may have multiple occurrences of the same event type.

Seven of the 34 patients who required device explantation were considered candidates for future re-implantation.

International Marketing Surveillance

According to the AMS Patient Information Form (PIF) database, 460 Acticon™ Neosphincters were implanted worldwide from May 1996 through January 2001. The PIF is a form which is completed by the hospital at the time of revision surgery and is *encouraged* by the sponsor to be returned but not required. During this time period, 119 revisions were reported in 94 patients following the original implant of the device. Reasons for revision were recorded for 85 of these procedures and included fluid loss (18), erosion (16), infection (15) and recurring incontinence (14).

XI. CONCLUSIONS DRAWN FROM STUDIES

Preclinical studies assessed the device design, mechanical properties, reliability, and materials biocompatibility. Results from this testing provide assurance that the device design is appropriate for the intended use.

Results from the pivotal clinical trial indicate that slightly over one-half (51.3%) of all patients who were implanted with the Acticon™ Neosphincter for severe fecal incontinence had a resolution or clinically significant reduction in their symptoms after one year. For the subset of patients who were able to maintain a functional device for 12 months, approximately 85% had meaningful improvements in their incontinence. In addition, quality of life measures showed improvement in many of these latter patients.

A majority of the patients implanted experienced at least one device-related adverse event. Besides pain, the two most common adverse events were infection (31% of implanted patients) and device erosion (21%). Surgical intervention was required to address 36% of these adverse events. Half (50%) of the implanted patients required at least one additional surgical device revision after the original implantation procedure and 30% required total device explantation due to adverse events.

XII. PANEL RECOMMENDATIONS

The PMA was referred to the Gastroenterology and Urology Devices Advisory Panel for review and recommendations on August 17th, 2001. The panel recommended 7-1 that the application be approved subject to submission to, and approval by, the Center for Devices and Radiological Health (CDRH) of revised physician and patient labeling, revised indications for use (for patients 18 and older), a formal physician training program, and an agreement to conduct a 12-month post-market follow-up study of those patients already enrolled in the pivotal clinical trial. The panel recommended that patients under the age of 18 continue to be evaluated and receive the device, if clinically indicated, under HDE provisions.

XIII. CDRH DECSISION

CDRH concurred with the Panel's recommendations. The applicant addressed all issues raised by the Panel and CDRH. Based on the information provided in the PMA, CDRH has determined that the Acticon™ Neosphincter is safe and effective for the indication of treatment of severe fecal incontinence in males and females eighteen years and older who have failed, or are not candidates for, less invasive forms of restorative therapy. FDA inspection of the manufacturing facilities determined that the applicant was in compliance with the Quality Systems Regulation {21CFR820}.

XIV. APPROVAL SPECIFICATIONS

Professional Labeling.

- Acticon™ Neosphincter, Package Insert
- Acticon™ Neosphincter Operating Room Manual

Patient Labeling

- Acticon™ Neosphincter Patient Information Brochure

Hazards to Health from Use of the Device

See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Post-approval Requirements and Restrictions

See approval order